Novel Promising Benzoazacrown Ethers as a Result of Ring Transformation of Benzocrown Ethers: Synthesis, Structure, and Complexation with Ca^{2+}

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A series of promising benzoazacrown ethers with the nitrogen atom conjugated with the benzene ring were synthesized using a novel synthetic procedure based on stepwise transformation of the macroheterocycle. The structures and spectral properties of the resulting benzoazacrown ethers and their complexes with Ca^{2+} were studied by X-ray diffraction and ^1H, ^{13}C, and ^{15}N NMR spectroscopy including the 2D NOESY technique.
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Introduction

Crown compounds are capable of selective binding of metal ions, organic compounds, and neutral molecules. This capability underlies the use of crown compounds as selective ligands for metal cations,[1] including fluorescent and photochromic ligands,[2] for the extraction and separation of metal cations,[3] for ion transport through membranes, in ion selective electrodes,[4] as phase-transfer catalysts and synzymes that model enzyme activity,[5] and so on.

While vigorous searches for new types of crown compounds capable of effective and selective complex formation in different media are in progress, the interest in crown compounds with a combination of O and N atoms as part of the macrocycle continues unabated.[6] These compounds exhibit complex-forming properties intermediate between those of crown ethers, which strongly bind alkali and alkaline earth metal ions, and those of cyclams, which form stable complexes with transition and heavy metal ions.

As regards the use of azacrown ether fragments in photosensitive ligands, those compounds in which the nitrogen atom can be conjugated with the chromophore are of special interest. Derivatives of *N*-phenylazacrown ethers and 1-aza-2,3-benzocrown ethers are important among these compounds, as they have the simplest structure. The latter belong to a poorly studied type of crown compound where most of the functional derivatives are almost inaccessible. Only individual syntheses of some 1-aza-2,3-benzocrown ether derivatives have been described, based on macrocycle construction from two acyclic moieties (so-called 1+1 condensation).[7]

Meanwhile, apart from construction from several fragments, methods for ring construction based on ring opening followed by the use of the resulting acyclic compounds in the synthesis of new heterocycles have been proposed for many heterocycles, e.g., for pyridine.[8] However, examples of crown ether ring opening are sparse.[9] Nevertheless, synthesis of new crown compounds from podands resulting from ring opening in available crown ethers, used as synthons, appears in some cases to be a good alternative to existing methods of synthesis of heterocyclic compounds.[10]

Results and Discussion

Synthesis of Benzoazacrown Ethers: We have previously shown[11] that heating formylbenzocrown ethers **1a**−**c**[12] with an ethanol solution of $MeNH_2$ and $MeNH_3^+Cl^-$ yields nitrogen-containing podands **2a**−**c** in 66−80% yields (Scheme 1). This reaction was the first example of crown ether opening under the action of an N-nucleophile.

Owing to the presence of the secondary amino group and the terminal hydroxy group in podands **2a**−**c**, we were able

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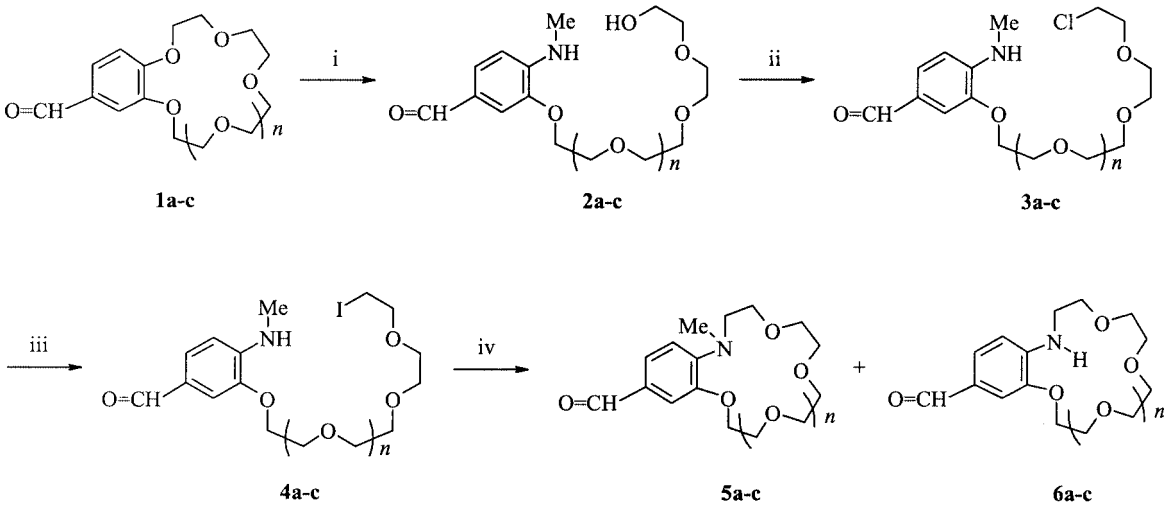


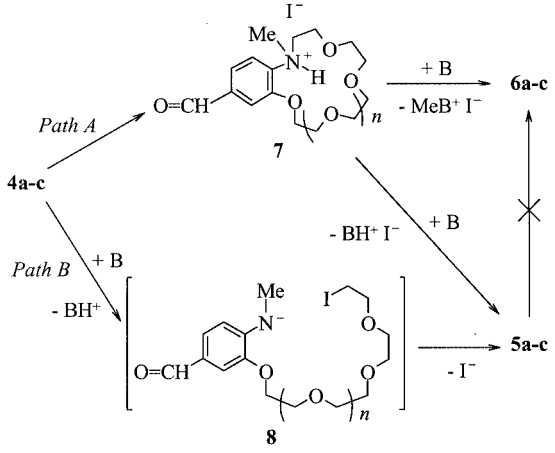
Scheme 1. Reagents and conditions: (i) $MeNH_2/MeNH_3^+Cl^-$/EtOH, sealed tube, 200 °C, 60 h (66−78%); (ii) $SOCl_2$/pyridine/$CHCl_3$, reflux, 6 h (92−97%); (iii) NaI/acetone, reflux, 80−100 h (75−97%); (iv) M_2CO_3 (M = Li, Na, K, Rb, Cs)/MeCN, sealed tube, 100 °C, 150 h (**5a**−**c**: 53−67%; **6a**−**c**: 11−18%)

to develop a method for cyclization of these compounds into previously unknown *N*-methylbenzoazacrown ethers **5a**−**c**. For successful cyclization, the hydroxy group had to be replaced by a good leaving group. In the syntheses of azacrown ethers by condensation of two fragments, iodine is frequently used as such a group.[6] Therefore, initially, we obtained chloro derivatives **3a**−**c** in 92−97% yields by the reaction of podands **2a**−**c** with $SOCl_2$ in the presence of pyridine. Then they were made to react with NaI to replace the chlorine atom in **3a**−**c** by an iodine atom in 75−97% yields. Heating of iodo derivatives **4a**−**c** in acetonitrile in the presence of alkali metal carbonates for 150 h resulted in the formation of benzoazacrown ethers **5a**−**c** in 53−67% yields. As well as *N*-methylbenzoazacrown ethers **5a**−**c**, benzoazacrown ethers **6a**−**c** were also formed in 11−18% yields.

The cyclization time we used is the optimum. Although iodides **4a**−**c** are not consumed completely during this period, longer times result in markedly lower yields of **5a**−**c** owing to substantial resinification of the reaction mixture.

The structures of all the obtained compounds were established by ^1H and ^{13}C NMR spectroscopy and confirmed by high-resolution mass spectrometry and elemental analysis.

We were interested to study in detail the key step of the synthesis of benzoazacrown ethers **5a**−**c**, i.e. cyclization of **4a**−**c**. This process may occur either as an intramolecular N-alkylation of the secondary amino group to give a macrocyclic ammonium salt **7** (*path A*) or via the intermediate formation of anion **8** (*path B*), which takes place on treatment with a base by abstraction of a proton from the amino group. In the former case, the reaction ends in deprotonation of ammonium salt **7** under the action of a base. The second path involves intramolecular nucleophilic replacement of iodine atom in **8** by the negatively charged nitrogen atom to give the macroheterocycle (Scheme 2).



Scheme 2. Putative intermediates and the corresponding paths of transformation of iodo derivatives **4** into benzoazacrown ethers **5** and **6**

The reaction along *path A* is expected to be slow because the nitrogen atom in iodides **4a**−**c** is relatively inert toward *N*-alkylation as its lone electron pair is conjugated with the electron-withdrawing formyl group. In terms of this variant, the formation of **5a**−**c** and **6a**−**c** can be interpreted as the simultaneous occurrence of *N*-deprotonation and *N*-demethylation reactions. The latter reaction is encountered in the series of substituted ammonium salts.[13]

If the reaction follows *path B*, the presence of the electron-withdrawing formyl group in **4a**−**c** should facilitate the formation of anion **8**. Cyclization with intermediate formation of the anion, if it is formed in a sufficient amount, is expected to be fast because the negatively charged nitrogen atom is a better nucleophile than the neutral one. In addition, one could expect a positive or negative template

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effect[14] of the metal cation, which can act as the counterion for anion **8**. *Path B* appears plausible when selective formation of **5a−c** is involved, because direct elimination of the methyl group (without preliminary protonation of **5**) under the action of the base to give **6a−c** seems unlikely.

In order to accumulate data that would allow us to make a reliable choice of the cyclization mechanism, we carried out a series of experiments under comparable conditions; the reaction time (150 h) was usually insufficient for complete transformation of **4a−c** into reaction products. Data on the recovery of starting compounds **4a−c** and the yields of benzoazacrown ethers **5a−c** are presented in Table 1.

Table 1. Cyclization of iodides **4a−c** into benzoazacrown ethers **5a−c** and **6a−c** under the action of M_2CO_3

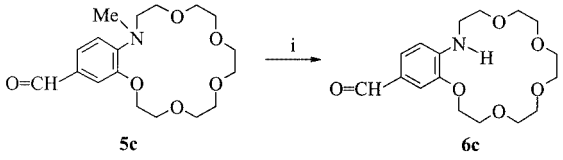
Iodide[a]	M	Recovery of **4** [%]	Yield [%][b] [c]	
			5	**6**
4a	Li	10	67	12
	Na	8	61	11
	K	14	65	8
	Rb	10	67	9
	Cs	3	53	5
	−	8	24	41
4b	Li	17	55	18
	K	20	61	11
	Na	20	53	11
	Rb	14	53	1
	Cs	0	25	2
	−	8	12	53
	− [d]	6	65	1
4c	Li	37	53	11
	Na	35	52	2
	K	32	53	3
	Rb	26	53	2
	Cs	0	0	0
	−	23	0	42

[a] In MeCN, 100 °C (sealed tube) for 150 h. [b] The ratio and the yields of the reaction products were found from ^{1}H NMR spectra. [c] Calculated with respect to converted **4a−c**. [d] In the presence of BDN.

We found that the recovery of iodopodands **4** rises and the yields of *N*-methylbenzoazacrown ethers **5** regularly decrease with an increase in the length of the oligoethylene glycol chain in **4**. This was to be expected in a situation where the steric strain does not play a crucial role in the formation of the macrocycle and the template effect of the metal cation is weak. Indeed, the size of the metal cation (except for Cs^+) does not exert a pronounced influence on the cyclization of podands **4a−c**, since the recovery of **4a−c** and the yields of **5a−c** are comparable for different metal carbonates. In the case of Cs_2CO_3, we encountered a clear-cut negative effect on the cyclization; the reaction mixture was considerably resinified, resulting in low yields of **5a,b**, while crown ether **5c** was not formed at all. When a non-nucleophilic organic base, 1,8-bis(dimethylamino)naphthalene (BDN), incapable of template interaction with podand **4b**, was used instead of a metal carbonate, the yield of **5b** substantially increased and only traces of **6b** were formed (Table 1). To summarize the influence of metal carbonates, we conclude that coordination of a metal cation to podands **4a−c** has an adverse effect on the efficiency of cyclization; this is to be expected when the reaction involves the formation of a macrocyclic ammonium cation (*path A*).

The regularities of formation of benzoazacrown ethers **6a−c** are also of considerable interest in view of the probable cyclization routes for podands **4a−c**. Thus we found that the highest yields of **6** were always formed when the weakest base, Li_2CO_3, was used. This suggests that conducting the reaction in the absence of a base might further increase the yield of **6**. To verify this hypothesis, we carried out cyclization of iodides **4a−c** in the absence of metal carbonates. The degrees of conversion of **4a−c** into the reaction products were virtually the same as in experiments with M_2CO_3, but the ratio of the yields of **5** and **6** markedly changed towards the latter; **6c** even became the only product of cyclization of **4c**. Apparently, the absence of a base resulted in a significant increase in the content of the intermediate macrocyclic cation **7**, whose demethylation furnishes **6**.

Since protonation of *N*-methylbenzoazacrown ether **5** should give rise to macrocyclic cation **7**, one would expect that **5** would be converted into **6** on treatment with an acid. To confirm this assumption, we heated **5c** in the presence of acetic acid. TLC monitoring did indeed show that, under these mild conditions, the initial *N*-methylbenzoazacrown ether **5c** was slowly converted into **6c** (Scheme 3).



5c **6c**

Scheme 3. Reagents and conditions: (i) AcOH/EtOAc, reflux, 80 h (35%)

Thus, the whole set of data concerning the cyclization of iodides **4a−c** into benzoazacrown ethers **5a−c** and **6a−c** indicates that the reaction follows *path A*. Apparently, realization of *path B* is prevented by the fact that M_2CO_3 is not sufficiently basic to deprotonate the amino group in **4a−c**, despite the electron-withdrawing properties of the formyl group located in the *para*-position to the nitrogen atom.

X-ray Crystallography: The structures of benzoazacrown ethers **5a** and **6c** were determined by X-ray diffraction analysis. The general view and atom numbering scheme for molecule **5a** are shown in Figure 1. Compound **6c** crystallizes as a hydrate and the crystal contains two crystallographically independent molecules of the benzoazacrown ether and three water molecules. Figure 2 shows all structural units of the crystal with atom numbering. The crystal data and structure-refinement parameters for **5a** and **6c** are given in Table 2; selected bond lengths and angles are given in Supporting Information (Tables 1S and 2S, For Supporting Information see also the footnote on the first page of this article).

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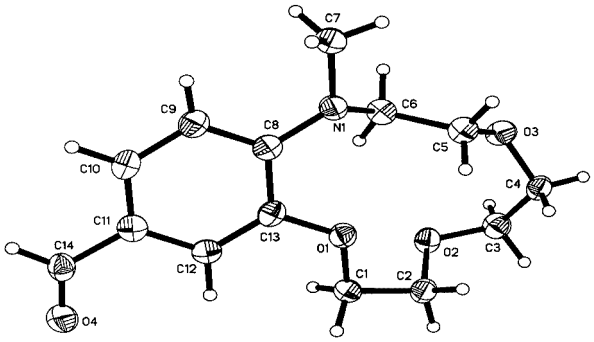


Figure 1. Structure of compound **5a**

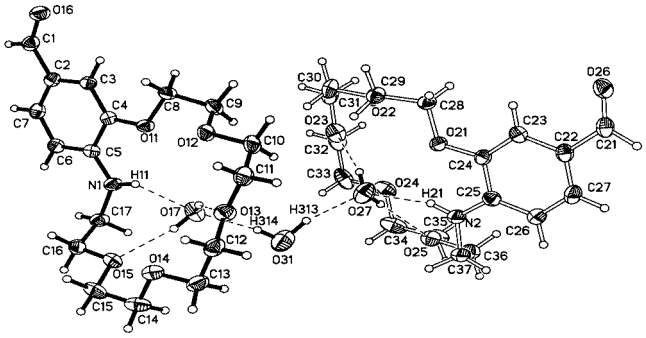
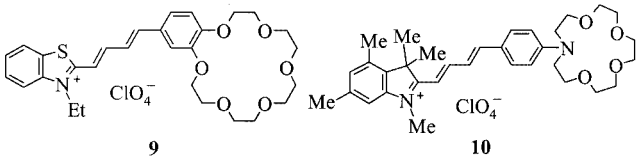


Figure 2. Structure and mutual arrangement of two independent molecules of compound **6c** and three water molecules of crystallization. The second molecule of **6c** is drawn with open lines for clarity. The hydrogen bonds are shown with dashed lines.

In molecule **5a**, the benzene ring displays some bond length disturbance. The C−C bond common to two rings (benzene and crown ether) is elongated in this molecule; the C(8)−C(13) bond length in **5a** is equal to 1.422(3) Å (the standard value is 1.399 Å). The same peculiarity is characteristic of **6c**. The corresponding bond lengths [C(4)−C(5) and C(24)−C(25)] in the independent molecules of **6c** are also elongated to 1.435(2) Å (both). Somewhat less pronounced elongation of this bond is observed in 18-crown-6 ether butadienyl dye **9** based on *N*-ethyl-substituted benzothiazolium perchlorate;[15] the bond length is 1.414(4) Å.



9 **10**

Table 2. Crystal data, data collection, structure solution and refinement parameters for **5a** and **6c**

Compound	**5a**	**6c**
Empirical formula	$C_{14}H_{19}NO_4$	$C_{17}H_{28}NO_{7.5}$
Molecular mass	265.30	366.40
Color, habit	colorless, block	colorless, block
Crystal size [mm]	0.30 × 0.20 × 0.20	0.40 × 0.20 × 0.10
Crystal system	orthorhombic	monoclinic
Space group	$P2_12_12_1$	$P2_1/c$
Unit cell dimensions		
a (Å)	6.8218(4)	22.4437(3)
b (Å)	12.1261(8)	8.5017(1)
c (Å)	15.951(1)	21.8153(3)
α [°]	90	90
β [°]	90	116.512(1)
γ [°]	90	90
Volume [Å^3]	1319.5(1)	3724.83(8)
Z	4	8
Density (calcd.) [g/cm^3]	1.336	1.307
μ(Mo-K_α) [mm^{-1}]	0.098	0.102
F(000)	568	1576
Diffractometer	Bruker SMART CCD	
Temperature [K]	110.0(2)	120.0(2)
Radiation [λ, Å]	graphite-monochromatized Mo-K_α (0.71073)	
θ range for data collection [°]	2.11 ≤ θ ≤ 27.00	1.01 ≤ θ ≤ 28.00
Index ranges	−8 ≤ *h* ≤ 8	−29 ≤ *h* ≤ 29
	−15 ≤ *k* ≤ 13	−11 ≤ *k* ≤ 11
	−20 ≤ *l* ≤19	−28 ≤ *l* ≤ 27
Reflections collected	8988	28891
Independent reflections, *R*(int)	2882, 0.0586	8988, 0.0357
Data reduction	Bruker SAINT	
Absorption correct.	not applied	not applied
Data/parameters	2808/248	8988/685
Goodness-of-fit on F^2	0.979	1.023
Final *R*1, *wR*2 [$I > 2\sigma(I)$]	0.0528, 0.1250	0.0385, 0.0948
*R*1, *wR*2 (all data)	0.0623, 0.1306	0.0797, 0.1076
Largest diff. peak/hole [e·Å^{-3}]	0.328/−0.206	0.292/−0.221

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One could explain this elongation as being due to steric hindrance between the two oxygen atoms in the adjacent positions of the benzene ring. The distance between these oxygen atoms in **9** is equal to 2.59 Å, which is shorter than twice the van der Waals radius (2.8 Å) of oxygen atom. However, in such a case not only the elongation of the C−C bond but also appropriate distortion of the $O-C_{(Ar)}-C_{(Ar)}$ bond angles should be expected. A distortion of these angles is actually found. However, this distortion has the opposite pattern: two internal O−C−C angles are reduced (≈ 115°), whereas two external O−C−C angles are increased (≈ 125°). These ring distortions, together with the aforementioned elongation of the C−C bond, have been rationalized within the concept of conjugation of the lone electron pair (LEP) in the p orbital of oxygen with the π-system of the benzene ring.[16] The bond angles at these atoms (≈ 118°) imply the sp^2 hybridization state, unlike the bond angles at the other oxygen atoms of the crown ether moiety (≈ 112°) which are typical of the sp^3 hybridization state. Moreover, the $C-O-C_{(Ar)}-C_{(Ar)}$ torsion angles are close to 180 or 0°.

Similar geometric peculiarities are observed in **5a** and **6c**. The O(1)···N distance (2.72 Å in **5a**, and 2.57−2.58 Å in **6c**) is shorter than the sum of the van der Waals radii of the N and O atoms (3.0 Å). The bond angle at the O(1) atom [118.3(2)° in **5a**, and 116.6(1), 117.2(1)° in **6c**] is greater than the bond angles at the other crown ether oxygen atoms [113.5(2)−115.7(2) and 110.5(1)−113.7(1)°, respectively], and the $C-O(1)-C_{(Ar)}-C_{(Ar)}$ torsion angles (18.3, and 0.5, 4.6°, respectively) are suitable for conjugation. In these structures, the C(1)···C(12) in **5a**, or C(3)···C(8) and C(23)···C(28) in **6c** distances are rather short (2.83, or 2.83 and 2.82 Å, respectively); thus, the conjugation is accomplished in spite of essential steric hindrances.

The nitrogen atom in **5a** has a nonsymmetric pyramidal bond configuration. The bond angles vary within 114.0(2)−119.6(2)°; the C(6)−N(1)−C(8)−C(9) torsion angle is equal to −139.7°; the $N-C_{(Ar)}$ bond length is equal to 1.389(3) Å. The geometry of the crown ether moiety observed in **5a** in the vicinity of the N atom does not provide appropriate conditions for the involvement of the nitrogen atom LEP in effective conjugation with the benzene ring π-system.

The geometry about the nitrogen atom in **5a** is different from that observed in aza-15-crown-5 ether butadienyl dye **10** based on indolium perchlorate.[17] In **10**, the nitrogen atom has a planar geometry and this plane is virtually coplanar to the benzene ring. The LEP of the nitrogen atom is involved in the conjugation with the benzene ring. This fact is obvious in view of the pronounced *para*-quinoid pattern of the bond length distribution. Exactly the same situation is observed in **6c**. Both independent molecules exhibit a pronounced *para*-quinoid pattern of bond length distribution like that in **10**. Two opposite bonds in the benzene ring of both molecules [C(3)−C(4), C(6)−C(7), and C(23)−C(24), C(26)−C(27)] are substantially shortened [1.367(2), 1.388(2), and 1.366(2), 1.386(2) Å] compared to other bonds in the rings [1.393(2)−1.435(2) and 1.392(2)−1.435(2) Å]. The $N-C_{(Ar)}$ bond lengths [1.353(2) and 1.352(2) Å] are shorter than that found in molecule **5a**. In addition, the sums of the bond angles at the nitrogen atoms (close to 360°) and the C(17)−N(1)−C(5)−C(6) and C(37)−N(2)−C(25)−C(26) torsion angles (−4.6 and −7.5°, respectively) fit best the geometry for the conjugation of LEP of the nitrogen atoms with the corresponding benzene ring. In the crystal of **6c**, three water molecules are involved in a system of hydrogen bonds with each other, the N−H groups, and the oxygen atoms of the crown ether moieties (Figure 2).

NMR Spectroscopy: NMR spectroscopy provides detailed information on the structure of crown compounds and the composition, structure, and strength of their complexes in solutions.[18] Comparison of the positions of signals in the ^1H and ^{13}C NMR spectra in CD_3CN solution for the series of benzoazacrown ethers **5a−c** and **6a−c** clearly points to differences between their structures (see Supporting Information, Tables 3S and 4S). Thus downfield shifts of 0.15−0.28 ppm of the C(3)−H proton signal, 0.07−0.09 ppm of the formyl proton signal, and of 5.8−8.3 ppm of the C(3) carbon were observed for *N*-methylbenzoazacrown ethers **5** with respect to demethylated derivatives **6** with the same macrocycle size (the numbering of H and C atoms differing from that dictated by the IUPAC rules is shown in Scheme 4). This implies a lower degree of conjugation of the nitrogen LEP with the benzene ring in **5a−c**, which may be due to rotation of the $N(Me)CH_2$ fragment about the Ar−N bonds caused by substantial steric interaction with the $CH_2O_{(Ar)}$ fragment located in the *ortho*-position. Indeed, the NOE spectra of benzoazacrown ethers **5a−c** showed that, in solution, the methyl group is closer in space to the C(3)−H proton than the N-methylene group. These facts are in good agreement with the X-ray diffraction data for **5a** in which the shortest $C(3)-H\cdots H_3CN$ and $C(3)-H\cdots H_2CN$ distances are 2.31 and 4.15 Å, respectively. Hence, the conformation of the macrocycle fragment about the nitrogen atom does not change fundamentally on passing from the crystalline state to a solution. The NOE spectra of benzoazacrown ethers **6a−c** exhibit intense cross-peaks between the C(3)−H and CH_2N protons and no interactions between the C(3)−H and NH protons. These facts point to a high degree of conjugation of the nitrogen atom with the aromatic ring and to the fact that the NH group proton points inside the macroheterocycle and, perhaps, forms hydrogen bonds with some of the crown-ether oxygen atoms.

We obtained interesting results when investigating the positions of nitrogen atom signals in the ^{15}N NMR spectra of benzoazacrown ethers **5** and **6** (Table 3). It was found that with an increase in the macrocycle size over the series of compounds **5**, δ_N regularly shifts upfield, indicating an increase in the sp^3-hybrid (pyramidal) character of the nitrogen atom. Conversely, an increase in the macrocycle size in compounds **6** entails a downfield shift in δ_N, the lowest-field δ_N value being observed for the model phenylaza-15-crown-5 ether **11**. This is, apparently, related to the increase

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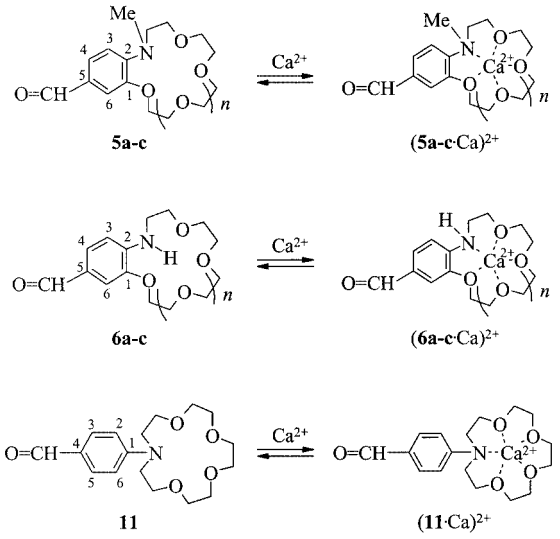

Scheme 4. Complex formation of azacrown ethers **5**, **6**, and **11** with Ca^{2+} ions

in the sp^2-hybrid character of the nitrogen atom caused by increased conjugation of the nitrogen atom LEP with the benzene ring π-system.

Table 3. ^{15}N NMR chemical shifts for azacrown ethers **5a−c**, **6a−c**, and **11** and for their complexes with $Ca(ClO_4)_2$

Ligand[a]	5a	5b	5c	6a	6b	6c	11
δ_L	−318.5	−325.8	−328.5	−315.3	−315.9	−309.5	−303.7
$\delta_{(L\cdot Ca)}$	−332.3	−334.7	−335.1	−316.2	−326.3	−322.1	−306.8
$\Delta\delta$[b]	−13.8	−8.9	−6.6	−0.9	−10.4	−12.6	−3.1

[a] CD_3CN at ambient temperature, c_L = 0.15 M, c_{Ca} = 0.75 M. [b] $\Delta\delta = \delta_{(L\cdot Ca)} - \delta_L$ [ppm].

Thus, the marked decrease in the conjugation of the nitrogen atom with the benzene ring and its pyramidal geometry allow us to predict a high capacity for complexation with metal cations for *N*-methylbenzoazacrown ethers **5a−c**, whereas the participation of the nitrogen LEP in conjugation and the position of the hydrogen atom inside the macroheterocycle can become serious obstacles to efficient complexation for benzoazacrown ethers **6a−c**.

We carried out a comparative study of the complexing ability with respect to Ca^{2+} ion of our synthesized compounds **5a−c** and **6a−c** and of the formyl derivatives of phenylazacrown ether **11**, widely used in the synthesis of chromoionophores. The Ca^{2+} ion was chosen as it forms NMR-spectroscopically detectable complexes with all the tested compounds. The addition of excess Ca^{2+} ions to solutions of benzoazacrown ethers **5** and **6** induces substantial changes in the ^1H and ^{13}C NMR spectra, indicating complex formation (Scheme 4; Tables 3S and 4S in Supporting Information). The presence of a two-charged cation in the crown ether cavity entails downfield shifts of the signals of most protons: by δ = 0.18−0.43 ppm for CH_2O groups, by δ = 0.21−0.34 ppm for the C(4)−H and C(6)−H aromatic protons, and by δ = 0.09−0.16 ppm for the formyl group protons. An especially great downfield shift $\Delta\delta_H$ (0.50−0.77 ppm) is found for the signals of the C(3)−H protons located in the *ortho*-position relative to the nitrogen atom; evidently this reflects further switching of its LEP from conjugation with the benzene ring to coordination to the Ca^{2+} cation. A similar conclusion can be drawn by analyzing the changes in the carbon chemical shifts for benzoazacrown ethers **5** and **6**. The greatest downfield shifts on complexation were observed for the carbon signals from C(3) (δ = 5.4−16.5 ppm), C(5) (δ = 5.1−8.5 ppm), and C=O (δ = 3.1−4.5 ppm). The signals of most carbon atoms of the CH_2O groups shift upfield by δ = 0.2−2.3 ppm, which is a typical behavior of crown ethers.[18] It is noteworthy that the proton signals of the MeN and CH_2N groups also shift upfield upon complexation. This might be due to the overall effect from the change in the macrocycle conformation on binding to the metal cation and to the increase in the contribution of the sp^3-hybrid state for the nitrogen atom. However, the changes in the carbon chemical shifts for these groups do not follow a well-marked trend, which rather implies a conformational dependence for $\Delta\delta_C$.

For comparison, the ^1H and ^{13}C chemical shifts of model compound **11** and its complex with Ca^{2+} were also measured (see Tables 3S and 4S in Supporting Information). Complexation of **11** gives rise to $\Delta\delta_H$ and $\Delta\delta_C$ values similar in magnitude and direction to the corresponding values for benzoazacrown ethers **5** and **6**. Thus, the LEP of the nitrogen atom in **11** also switches from effective conjugation with the benzene ring in the free ligand to coordination of the calcium atom in the complex.

Complexation with Ca^{2+} ions induces upfield shifts of the nitrogen signals in the ^{15}N NMR spectra of all azacrown ethers (Table 3). Apparently, in the case of **5**, **6**, and **11**, complex formation decreases the electron-withdrawing effect of the benzene ring and increases the contribution of the sp^3-hybrid state for the nitrogen atom, and these effects prevail over the possible decrease in electron density caused by involvement of the nitrogen LEP in coordination to the metal cation. In addition, in the case of **5a−c**, the δ_N values for the complexed ligands become closer to each other, about −334 ppm, and the changes in the chemical shifts $\Delta\delta_N$ markedly diminish as the macrocycle size grows. This might indicate that the degree of pre-organization of **5** for binding of a metal cation increases with an increase in the macrocycle size, because the changes in the pyramidal geometry of the nitrogen atom induced by complexation become less and less pronounced over the series from **5a** to **5c**. An opposite situation is found in the case of **6a−c**. The changes in the $\Delta\delta_N$ chemical shifts increase with an increase in the macrocycle size; this may be due to the fact that the macrocycle rearrangement needed for incorporation of the Ca^{2+} cation into the crown ether cavity instead of hydrogen becomes more pronounced on passing from **6a** to **6c**.

The whole set of obtained data allows us to predict that *N*-methylbenzoazacrown ethers **5a−c** as ligands can have

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substantial advantages not only over benzoazacrown ethers **6a−c**, in which the crown-ether cavity is blocked by the hydrogen atom pointing therein, but also over the well-known phenylazacrown ether derivatives in which the nitrogen atom is less accessible for coordination to the metal cation owing to more effective conjugation with the benzene ring.

Conclusion

Thus, we developed a new approach to the synthesis of benzoazacrown ethers based on accessible formyl derivatives of benzocrown ethers, which are used as synthons. This approach consists in stepwise transformation of the macroheterocycle and makes it possible to prepare previously unknown benzoazacrown ether derivatives for investigation. The presence of the nitrogen atom conjugated to the benzene ring opens up extensive opportunities for the synthesis of promising new groups of ion selective dyes, luminophores, and photochromic ionophores for membrane transport and photocontrolled extraction.

Experimental Section

General Remarks: Melting points [°C] were determined with a MEL-Temp II apparatus in a capillary and are uncorrected. 1D ^{1}H and ^{13}C NMR spectra were recorded with a Bruker DRX500 instrument (500.13 and 125.76 MHz, respectively) as solutions in $CDCl_3$ or CD_3CN using the solvent as an internal reference (δ = 7.27 and 1.96 ppm for ^{1}H, and δ = 77.00 and 118.10 ppm for ^{13}C, respectively); 2D homonuclear ^{1}H-^{1}H COSY and NOESY spectra and heteronuclear ^{1}H-^{13}C COSY (HSQC and HMBC) spectra were used to assign the proton and carbon signals; 2D heteronuclear ^{1}H-^{15}N COSY spectra (50.69 MHz for ^{15}N) in CD_3CN solutions were recorded to establish the ^{15}N chemical shifts using the solvent as an internal reference (δ = −137.1 ppm). IR spectra of film on a KBr glass were recorded with Shimadzu IR-470 and Bruker IFS-113V spectrophotometers. Mass spectra were measured with a Varian MAT-311A instrument and high-resolution mass spectra were recorded with Finnigan MAT-95-XL and Finnigan MAT-8430 instruments (perfluoroparaffin as a standard) with direct sample inlet into the ionization zone; the energy of ionizing electrons was 70 eV. Elemental analyses were performed at the microanalytical laboratory of the A. N. Nesmeyanov Institute of Organoelement Compounds in Moscow, Russia. The course of the reactions was monitored by TLC (Merck, DC-Alufolien, Aluminiumoxid 60-F_{254}, neutral, Typ E, and Kieselgel 60-F_{254} plates). Column chromatography was performed with Merck Kieselgel 60 (0.063−0.100 mm). Formylbenzocrown ethers **1a−c**[12] and *N*-(4-formylphenyl)aza-15-crown-5 ether (**11**)[19] were prepared according to published procedures. 1,8-Bis(dimethylamino)naphthalene and CD_3CN (water impurity < 0.05%) were purchased from Merck. $Ca(ClO_4)_2$ was dried under reduced pressure at 240 °C.

Synthesis of Podands 2a−c (General Procedure): Formylbenzocrown ether **1a−c** (7 mmol), $MeNH_3^+Cl^-$ (35 mmol), and a 35% solution of $MeNH_2$ in dry EtOH (25 mL) were heated at 200 °C (a bath with Wood's alloy) for 60 h in a sealed tube. After tube opening, the solvent was evaporated, 1.5% aqueous HBr (250 mL) was added to the residue, and the mixture was kept for 3 h. A 5% aqueous solution of KOH was then added up to pH 10, and the mixture was extracted with $CHCl_3$. The extract was concentrated and the residue was purified by column chromatography on silica gel using a 20:1 benzene/EtOH solvent system. The podands **2a−c** were isolated as light yellow oils.

Podand 2a: The procedure for the reaction of **1a** with $MeNH_2$ to give **2a** was similar to that described above. Yield: 1.31 g (66%). ^{1}H NMR ($CDCl_3$, 25 °C): δ = 2.86 (br. s, 1 H, OH), 2.94 (d, $^3J_{H,H}$ = 5.1 Hz, 3 H, MeN), 3.65 (m, 2 H, C*H*$_2$CH$_2$OH), 3.70−3.76 (m, 6 H, 2 CH$_2$O, C*H*$_2$OH), 3.88 (m, 2 H, C*H*$_2$CH$_2$OAr), 4.23 (m, 2 H, C*H*$_2$OAr), 5.52 (br. q, 1 H, NH), 6.57 [d, $^3J_{H,H}$ = 8.1 Hz, 1 H, C(5)−H], 7.28 [d, $^4J_{H,H}$ = 1.5 Hz, 1 H, C(2)-H], 7.40 [dd, $^3J_{H,H}$ = 8.1, $^4J_{H,H}$ = 1.5 Hz, 1 H, C(6)-H], 9.68 (s, 1 H, CH=O) ppm. ^{13}C NMR ($CDCl_3$, 25 °C): δ = 29.43 (q, $^1J_{C,H}$ = 136.8 Hz, MeN), 61.65 (t, $^1J_{C,H}$ = 142.4 Hz, CH$_2$OH), 67.50 (t, $^1J_{C,H}$ = 144.3 Hz, *C*H$_2$OAr), 69.39 (t, $^1J_{C,H}$ = 140.3 Hz, *C*H$_2$CH$_2$OAr), 70.13 (t, $^1J_{C,H}$ = 141.5 Hz, CH$_2$O), 70.49 (t, $^1J_{C,H}$ = 139.7 Hz, CH$_2$O), 72.40 (t, $^1J_{C,H}$ = 142.7 Hz, *C*H$_2$CH$_2$OH), 107.04 [dd, $^1J_{C,H}$ = 159.6, $^2J_{C,H}$ = 5.0 Hz, C(5)], 107.88 [d, $^1J_{C,H}$ = 166.8 Hz, C(2)], 125.10 [dd, $^2J_{C,H}$ = 23.2, $^3J_{C,H}$ = 7.6 Hz, C(1)], 129.50 [d, $^1J_{C,H}$ = 161.5 Hz, C(6)], 145.40 [C(3)], 145.65 [C(4)], 190.22 (d, $^1J_{C,H}$ = 169.7 Hz, CH=O) ppm. IR (film on KBr): $\tilde{\nu}$ = 3392 (br., O−H, N−H), 1664 (C=O) cm^{-1}. MS (EI, 70 eV): *m*/*z* = 283 (100) [M$^+$], 219 (8), 195 (10), 152 (8), 151 (71), 150 (60), 148 (9), 133 (14), 122 (13), 94 (12), 89 (30). HRMS calcd. for $C_{14}H_{21}NO_5$ [M$^+$] 283.1419, found 283.1404.

Podand 2b: The procedure for the reaction of **1b** with $MeNH_2$ to give **2b** was similar to that described above. Yield: 1.70 g (74%). ^{1}H NMR ($CDCl_3$, 25 °C): δ = 2.91 (d, $^3J_{H,H}$ = 4.1 Hz, 3 H, MeN), 3.19 (br. s, 1 H, OH), 3.59 (m, 2 H, C*H*$_2$CH$_2$OH), 3.62−3.73 (m, 10 H, 4 CH$_2$O, C*H*$_2$OH), 3.85 (m, 2 H, C*H*$_2$CH$_2$OAr), 4.19 (m, 2 H, C*H*$_2$OAr), 5.58 (br. s, 1 H, NH), 6.53 [d, $^3J_{H,H}$ = 8.1 Hz, 1 H, C(5)-H], 7.24 [d, $^4J_{H,H}$ = 1.6 Hz, 1 H, C(2)-H], 7.37 (dd, $^3J_{H,H}$ = 8.1, $^4J_{H,H}$ = 1.6 Hz, 1 H, C(6)-H], 9.64 (s, 1 H, CH=O) ppm. ^{13}C NMR ($CDCl_3$, 25 °C): δ = 29.44 (q, $^1J_{C,H}$ = 136.2 Hz, MeN), 61.55 (t, $^1J_{C,H}$ = 142.2 Hz, CH$_2$OH), 67.55 (t, $^1J_{C,H}$ = 144.2 Hz, *C*H$_2$OAr), 69.47 (t, $^1J_{C,H}$ = 141.6 Hz, *C*H$_2$CH$_2$OAr), 70.07 (t, $^1J_{C,H}$ = 141.1 Hz, CH$_2$O), 70.32 (t, $^1J_{C,H}$ = 141.5 Hz, CH$_2$O), 70.43 (t, $^1J_{C,H}$ = 141.3 Hz, 2 CH$_2$O), 72.59 (t, $^1J_{C,H}$ = 140.2 Hz, *C*H$_2$CH$_2$OH), 106.99 [d, $^1J_{C,H}$ = 159.9 Hz, C(5)], 107.87 [d, $^1J_{C,H}$ = 163.5 Hz, C(2)], 125.07 [dd, $^2J_{C,H}$ = 23.4, $^3J_{C,H}$ = 7.5 Hz, C(1)], 129.52 [d, $^1J_{C,H}$ = 160.4 Hz, C(6)], 145.46 [C(3)], 145.71 [C(4)], 190.27 [d, $^1J_{C,H}$ = 170.0 Hz, CH=O] ppm. IR (film on KBr): $\tilde{\nu}$ = 3392 (br., O−H, N−H), 1662 (C=O) cm^{-1}. MS (EI, 70 eV): *m*/*z* = 327 (88) [M$^+$], 239 (16), 221 (15), 219 (14), 195 (18), 178 (15), 177 (19), 151 (100), 150 (70), 94 (15), 89 (59). HRMS calcd. for $C_{16}H_{25}NO_6$ [M$^+$] 327.1682, found 327.1671.

Podand 2c: The procedure for the reaction of **1c** with $MeNH_2$ to give **2c** was similar to that described above. Yield: 2.02 g (78%). ^{1}H NMR ($CDCl_3$, 25 °C): δ = 2.92 (br.d, $^3J_{H,H}$ = 5.1 Hz, 4 H, MeN, OH), 3.58 (m, 2 H, C*H*$_2$CH$_2$OH), 3.62−3.71 (m, 14 H, 6 CH$_2$O, C*H*$_2$OH), 3.85 (m, 2 H, C*H*$_2$CH$_2$OAr), 4.19 (m, 2 H, C*H*$_2$OAr), 5.35 (br. q, 1 H, NH), 6.54 [d, $^3J_{H,H}$ = 8.1 Hz, 1 H, C(5)-H], 7.25 [br. s, 1 H, C(2)-H], 7.38 [br.d, $^3J_{H,H}$ = 8.1 Hz, 1 H, C(6)-H], 9.66 (s, 1 H, CH=O) ppm. ^{13}C NMR ($CDCl_3$, 25 °C): δ = 29.47 (q, $^1J_{C,H}$ = 137.1 Hz, MeN), 61.60 (t, $^1J_{C,H}$ = 142.1 Hz, CH$_2$OH), 67.85 (t, $^1J_{C,H}$ = 144.1 Hz, *C*H$_2$OAr), 69.45 (t, $^1J_{C,H}$ = 140.9 Hz, *C*H$_2$CH$_2$OAr), 70.18 (t, $^1J_{C,H}$ = 141.0 Hz, CH$_2$O), 70.43 (CH$_2$O), 70.47 (t, $^1J_{C,H}$ = 141.2 Hz, 4 CH$_2$O), 72.48 (t, $^1J_{C,H}$ = 140.9 Hz, *C*H$_2$CH$_2$OH), 107.03 [dd, $^1J_{C,H}$ = 158.6, $^2J_{C,H}$ = 5.4 Hz, C(5)], 108.26 [d, $^1J_{C,H}$ = 160.6 Hz, C(2)], 125.26 [dd, $^2J_{C,H}$ = 23.4, $^3J_{C,H}$ = 7.5 Hz, C(1)], 129.32 [d, $^1J_{C,H}$ = 158.8 Hz, C(6)], 145.46

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[C(3)], 145.65 [C(4)], 190.21 (d, $^1J_{C,H}$ = 170.1 Hz, CH=O) ppm. IR (film on KBr): $\tilde{\nu}$ = 3392 (br., O-H, N-H), 1662 (C=O) cm^{-1}. MS (EI, 70 eV): *m/z* = 371 (100) [M^+], 178 (19), 164 (35), 163 (50), 151 (84), 150 (83), 149 (25), 136 (75), 121 (29), 89 (33), 80 (18). HRMS calcd. for $C_{18}H_{29}NO_7$ [M^+] 371.1944, found 371.1951.

Synthesis of Chlorides 3a−c (General Procedure): A solution of $SOCl_2$ (1.1 mL, 15.0 mmol) in $CHCl_3$ (10 mL) was slowly added to a solution of **2a−c** (2.7 mmol) and dry pyridine (0.25 mL, 3.0 mmol) in $CHCl_3$ (20 mL) cooled in an ice bath. The resulting solution was refluxed for 6 h. After cooling, 5% aqueous HCl (50 mL) was added and the resulting mixture was extracted with $CHCl_3$. The extract was washed with 5% aqueous Na_2CO_3 and then with water and concentrated. The residue was purified by column chromatography on silica gel using elution with EtOAc in the case of **3a** and with a 20:1 benzene/MeOH solvent system in the case of **3b,c**. The chlorides **3a−c** were isolated as light yellow oils.

Chloride 3a: The procedure for the reaction of **2a** with $SOCl_2$ to give **3a** was similar to that described above. Yield: 753 mg (93%). ^{1}H NMR ($CDCl_3$, 25 °C): δ = 2.92 (br. s, 3 H, MeN), 3.61 (t, $^3J_{H,H}$ = 5.8 Hz, 2 H, CH_2Cl), 3.69 (br. s, 4 H, 2 CH_2O), 3.74 (t, $^3J_{H,H}$ = 5.8 Hz, 2 H, C*H*$_2$CH$_2$Cl), 3.86 (m, 2 H, C*H*$_2$CH$_2$OAr), 4.20 (m, 2 H, C*H*$_2$OAr), 5.18 (br. s, 1 H, NH), 6.55 [d, $^3J_{H,H}$ = 8.1 Hz, 1 H, C(5)-H], 7.26 [d, $^4J_{H,H}$ = 1.2 Hz, 1 H, C(2)-H], 7.38 [dd, $^3J_{H,H}$ = 8.1, $^4J_{H,H}$ = 1.2 Hz, 1 H, C(6)-H], 9.67 (s, 1 H, CH=O) ppm. ^{13}C NMR ($CDCl_3$, 25 °C): δ = 29.49 (q, $^1J_{C,H}$ = 136.6 Hz, MeN), 42.69 (t, $^1J_{C,H}$ = 151.8 Hz, CH_2Cl), 67.93 (t, $^1J_{C,H}$ = 144.2 Hz, *C*H$_2$OAr), 69.49 (t, $^1J_{C,H}$ = 141.5 Hz, *C*H$_2$CH$_2$OAr), 70.48 (CH_2O), 70.55 (CH_2O), 71.28 (t, $^1J_{C,H}$ = 144.5 Hz, *C*H$_2$CH$_2$Cl), 107.09 [d, $^1J_{C,H}$ = 159.3 Hz, C(5)], 108.30 [d, $^1J_{C,H}$ = 158.5 Hz, C(2)], 125.34 [dd, $^2J_{C,H}$ = 23.5, $^3J_{C,H}$ = 7.7 Hz, C(1)], 129.28 [d, $^1J_{C,H}$ = 160.2 Hz, C(6)], 145.42 and 145.52 [C(3), C(4)], 190.18 (d, $^1J_{C,H}$ = 169.8 Hz, CH=O) ppm. IR (film on KBr): $\tilde{\nu}$ = 3380 (br., N−H), 1671 (C=O) cm^{-1}. MS (EI, 70 eV): *m/z* = 304 (7), 303 (41) [M^+ with ^{37}Cl], 302 (15), 301 (100) [M^+ with ^{35}Cl], 178 (8), 151 (53), 150 (46), 107 (20), 65 (13), 63 (24), 58 (43). HRMS calcd. for $C_{14}H_{20}ClNO_4$ ($M^{+\cdot}$with ^{35}Cl) 301.1081, found 301.1097.

Chloride 3b: The procedure for the reaction of **2b** with $SOCl_2$ to give **3b** was similar to that described above. Yield: 908 mg (97%). ^{1}H NMR ($CDCl_3$, 25 °C): δ = 2.95 (d, $^3J_{H,H}$ = 4.8 Hz, 3 H, MeN), 3.63 (t, $^3J_{H,H}$ = 5.9 Hz, 2 H, CH_2Cl), 3.68 (s, 4 H, 2 CH_2O), 3.71 (m, 4 H, 2 CH_2O), 3.75 (t, $^3J_{H,H}$ = 5.9 Hz, 2 H, C*H*$_2$CH$_2$Cl), 3.88 (m, 2 H, C*H*$_2$CH$_2$OAr), 4.22 (m, 2 H, C*H*$_2$OAr), 5.21 (br. q, 1 H, NH), 6.58 [d, $^3J_{H,H}$ = 8.1 Hz, 1 H, C(5)-H], 7.29 [d, $^4J_{H,H}$ = 1.4 Hz, 1 H, C(2)-H], 7.41 [dd, $^3J_{H,H}$ = 8.1, $^4J_{H,H}$ = 1.4 Hz, 1 H, C(6)-H], 9.69 (s, 1 H, CH=O) ppm. ^{13}C NMR ($CDCl_3$, 25 °C): δ = 29.48 (q, $^1J_{C,H}$ = 136.5 Hz, MeN), 42.63 (t, $^1J_{C,H}$ = 149.7 Hz, CH_2Cl), 67.99 (t, $^1J_{C,H}$ = 144.3 Hz, *C*H$_2$OAr), 69.43 (t, $^1J_{C,H}$ = 138.7 Hz, *C*H$_2$CH$_2$OAr), 70.50 (br., 3CH_2O), 70.56 (CH_2O), 71.22 (t, $^1J_{C,H}$ = 144.6 Hz, *C*H$_2$CH$_2$Cl), 107.06 [dd, $^1J_{C,H}$ = 159.4, $^2J_{C,H}$ = 4.5 Hz, C(5)], 108.39 [d, $^1J_{C,H}$ = 159.0 Hz, C(2)], 125.32 [dd, $^2J_{C,H}$ = 23.4, $^3J_{C,H}$ = 7.5 Hz, C(1)], 129.25 [d, $^1J_{C,H}$ = 159.0 Hz, C(6)], 145.42 [C(3)], 145.55 [C(4)], 190.15 (d, $^1J_{C,H}$ = 169.9 Hz, CH=O) ppm. IR (film on KBr): $\tilde{\nu}$ = 3400 (br., N-H), 1667 (C=O) cm^{-1}. MS (EI, 70 eV): *m/z* = 347 (30) [M^+ with ^{37}Cl], 345 (64) [M^+ with ^{35}Cl], 151 (91), 150 (90), 148 (42), 122 (39), 109 (49), 107 (90), 94 (54), 77 (42), 65 (83), 63 (100). HRMS calcd. for $C_{16}H_{24}ClNO_5$ ($M^{+\cdot}$with ^{35}Cl) 345.1343, found 345.1365.

Chloride 3c: The procedure for the reaction of **2c** with $SOCl_2$ to give **3c** was similar to that described above. Yield: 970 mg (92%). ^{1}H NMR ($CDCl_3$, 25 °C): δ = 2.93 (br. s, 3 H, MeN), 3.61 (t, $^3J_{H,H}$ = 5.9 Hz, 2 H, CH_2Cl), 3.63−3.71 (m, 12 H, 6 CH_2O), 3.73 (t, $^3J_{H,H}$ = 5.9 Hz, 2 H, C*H*$_2$CH$_2$Cl), 3.86 (m, 2 H, C*H*$_2$CH$_2$OAr), 4.20 (m, 2 H, C*H*$_2$OAr), 5.24 (br. s, 1 H, NH), 6.56 [d, $^3J_{H,H}$ = 8.1 Hz, 1 H, C(5)-H], 7.27 (d, $^4J_{H,H}$ = 1.3 Hz, 1 H, C(2)-H], 7.39 [dd, $^3J_{H,H}$ = 8.1, $^4J_{H,H}$ = 1.3 Hz, 1 H, C(6)-H], 9.67 (s, 1 H, CH=O) ppm. ^{13}C NMR ($CDCl_3$, 25 °C): δ = 29.53 (q, $^1J_{C,H}$ = 136.6 Hz, MeN), 42.65 (t, $^1J_{C,H}$ = 149.7 Hz, CH_2Cl), 68.02 (t, $^1J_{C,H}$ = 144.4 Hz, *C*H$_2$OAr), 69.48 (t, $^1J_{C,H}$ = 138.0 Hz, *C*H$_2$CH$_2$OAr), 70.49 (t, $^1J_{C,H}$ = 140.4 Hz, CH_2O), 70.56 (t, $^1J_{C,H}$ = 140.4 Hz, 5 CH_2O), 71.26 (t, $^1J_{C,H}$ = 143.8 Hz, *C*H$_2$CH$_2$Cl), 107.10 [d, $^1J_{C,H}$ = 159.5 Hz, C(5)], 108.40 [d, $^1J_{C,H}$ = 160.0 Hz, C(2)], 125.36 [dd, $^2J_{C,H}$ = 23.4, $^3J_{C,H}$ = 7.8 Hz, C(1)], 129.35 [d, $^1J_{C,H}$ = 159.3 Hz, C(6)], 145.47 [C(3)], 145.61 [C(4)], 190.23 (d, $^1J_{C,H}$ = 170.0 Hz, CH=O) ppm. IR (film on KBr): $\tilde{\nu}$ = 3380 (br., N-H), 1670 (C=O) cm^{-1}. MS (EI, 70 eV): *m/z* = 391 (17) [M^+ with ^{37}Cl], 389 (47) [M^+ with ^{35}Cl], 178 (28), 151 (86), 150 (92), 148 (29), 122 (26), 109 (31), 107 (80), 94 (29), 65 (63), 63 (100). HRMS calcd. for $C_{18}H_{28}ClNO_6$ ($M^{+\cdot}$with ^{35}Cl) 389.1605, found 389.1632.

Synthesis of Iodides 4a−c (General Procedure): A solution of **3a−c** (2.0 mmol) and NaI (6.0 g, 40 mmol) in dry acetone (35 mL) was refluxed for 80−100 h and the solvent was evaporated. Water (50 mL) was added to the residue and the system was extracted with $CHCl_3$. The solvent was evaporated from the extract and the residue was purified by column chromatography on silica gel using a 5:1 benzene/EtOAc solvent system for **4a** and EtOAc for **4b,c**. The iodides **4a−c** were isolated as light yellow oils.

Iodide 4a: The procedure for the reaction of **3a** with NaI to give **4a** was similar to that described above. Yield: 713 mg (91%). ^{1}H NMR ($CDCl_3$, 25 °C): δ = 2.92 (s, 3 H, MeN), 3.23 (t, $^3J_{H,H}$ = 6.8 Hz, 2 H, CH_2I), 3.64−3.70 (m, 4 H, 2 CH_2O), 3.74 (t, $^3J_{H,H}$ = 6.8 Hz, 2 H, C*H*$_2$CH$_2$I), 3.86 (m, 2 H, C*H*$_2$CH$_2$OAr), 4.20 (m, 2 H, C*H*$_2$OAr), 5.17 (br. s, 1 H, NH), 6.55 [d, $^3J_{H,H}$ = 8.1 Hz, 1 H, C(5)-H], 7.26 [d, $^4J_{H,H}$ = 1.4 Hz, 1 H, C(2)-H], 7.38 [dd, $^3J_{H,H}$ = 8.1, $^4J_{H,H}$ = 1.4 Hz, 1 H, C(6)-H], 9.67 (s, 1 H, CH=O) ppm. ^{13}C NMR ($CDCl_3$, 25 °C): δ = 2.84 (t, $^1J_{C,H}$ = 150.7 Hz, CH_2I), 29.55 (q, $^1J_{C,H}$ = 136.6 Hz, MeN), 67.92 (t, $^1J_{C,H}$ = 144.3 Hz, *C*H$_2$OAr), 69.50 (t, $^1J_{C,H}$ = 141.1 Hz, *C*H$_2$CH$_2$OAr), 70.11 (t, $^1J_{C,H}$ = 141.1 Hz, CH_2O), 70.46 (t, $^1J_{C,H}$ = 141.2 Hz, CH_2O), 71.83 (t, $^1J_{C,H}$ = 145.1 Hz, *C*H$_2$CH$_2$I), 107.08 [d, $^1J_{C,H}$ = 159.3 Hz, C(5)], 108.27 [d, $^1J_{C,H}$ = 156.4 Hz, C(2)], 125.33 [dd, $^2J_{C,H}$ = 23.5, $^3J_{C,H}$ = 7.5 Hz, C(1)], 129.26 [d, $^1J_{C,H}$ = 160.4 Hz, C(6)], 145.39 and 145.47 [C(3), C(4)], 190.16 (d, $^1J_{C,H}$ = 170.0 Hz, CH=O) ppm. IR (film on KBr): $\tilde{\nu}$ = 3401 (br., N-H), 1669 (C=O) cm^{-1}. MS (EI, 70 eV): *m/z* = 393 (82) [M^+], 199 (33), 162 (26), 155 (100), 151 (89), 150 (87), 149 (27), 148 (35), 122 (39), 94 (47), 58 (52). HRMS calcd. for $C_{14}H_{20}INO_4$ [M^+] 393.0437, found 393.0494.

Iodide 4b: The procedure for the reaction of **3b** with NaI to give **4b** was similar to that described above. Yield: 850 mg (97%). ^{1}H NMR ($CDCl_3$, 25 °C): δ = 2.95 (br. s, 3 H, MeN), 3.26 (t, $^3J_{H,H}$ = 6.9 Hz, 2 H, CH_2I), 3.65−3.74 (m, 8 H, 4 CH_2O), 3.75 (t, $^3J_{H,H}$ = 6.9 Hz, 2 H, C*H*$_2$CH$_2$I), 3.88 (m, 2 H, C*H*$_2$CH$_2$OAr), 4.22 (m, 2 H, C*H*$_2$OAr), 5.21 (br. s, 1 H, NH), 6.58 [d, $^3J_{H,H}$ = 8.1 Hz, 1 H, C(5)-H], 7.29 [d, $^4J_{H,H}$ = 1.4 Hz, 1 H, C(2)-H], 7.41 [dd, $^3J_{H,H}$ = 8.1, $^4J_{H,H}$ = 1.4 Hz, 1 H, C(6)-H], 9.70 (s, 1 H, CH=O) ppm. ^{13}C NMR ($CDCl_3$, 25 °C): δ = 2.84 (t, $^1J_{C,H}$ = 150.8 Hz, CH_2I), 29.58 (q, $^1J_{C,H}$ = 136.8 Hz, MeN), 67.95 (t, $^1J_{C,H}$ = 144.3 Hz, *C*H$_2$OAr), 69.52 (t, $^1J_{C,H}$ = 141.6 Hz, *C*H$_2$CH$_2$OAr), 70.14 (t, $^1J_{C,H}$ = 141.3 Hz, CH_2O), 70.56 (t, $^1J_{C,H}$ = 141.1 Hz, 2 CH_2O), 70.63 (t, $^1J_{C,H}$ = 140.1 Hz, CH_2O), 71.88 (t, $^1J_{C,H}$ = 144.5 Hz, *C*H$_2$CH$_2$I), 107.10 [d, $^1J_{C,H}$ = 159.1 Hz, C(5)], 108.27 [d, $^1J_{C,H}$ = 157.0 Hz, C(2)], 125.35 [dd, $^2J_{C,H}$ = 23.5, $^3J_{C,H}$ = 7.5 Hz, C(1)], 129.41 [d, $^1J_{C,H}$ = 159.8 Hz, C(6)], 145.46 and 145.57 [C(3), C(4)], 190.29 (d, $^1J_{C,H}$ = 170.3 Hz, CH=O) ppm. IR (film on KBr): $\tilde{\nu}$ = 3380 (br.,

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N-H), 1668 (C=O) cm^{-1}. MS (EI, 70 eV): *m/z* = 437 (76) [M^+], 199 (69), 178 (57), 162 (59), 155 (100), 151 (94), 150 (96), 148 (70), 94 (68), 77 (56), 63 (79). HRMS calcd. for $C_{16}H_{24}INO_5$ [M^+] 437.0699, found 437.0711.

Iodide 4c: The procedure for the reaction of **3c** with NaI to give **4c** was similar to that described above. Yield: 723 mg (75%). ^1H NMR ($CDCl_3$, 25 °C): δ = 2.92 (br. s, 3 H, MeN), 3.22 (t, $^3J_{H,H}$ = 6.9 Hz, 2 H, CH_2I), 3.62−3.70 (m, 12 H, 6 CH_2O), 3.72 (t, $^3J_{H,H}$ = 6.9 Hz, 2 H, CH_2CH_2I), 3.85 (m, 2 H, CH_2CH_2OAr), 4.19 (m, 2 H, CH_2OAr), 5.25 (br. s, 1 H, NH), 6.55 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H, C(5)-H], 7.25 [d, $^4J_{H,H}$ = 1.6 Hz, 1 H, C(2)-H], 7.38 [dd, $^3J_{H,H}$ = 8.1, $^4J_{H,H}$ = 1.6 Hz, 1 H, C(6)-H], 9.66 (s, 1 H, CH=O) ppm. ^{13}C NMR ($CDCl_3$, 25 °C): δ = 2.86 (t, $^1J_{C,H}$ = 150.8 Hz, CH_2I), 29.51 (q, $^1J_{C,H}$ = 136.5 Hz, MeN), 67.96 (t, $^1J_{C,H}$ = 144.2 Hz, CH_2OAr), 69.43 (CH_2CH_2OAr), 70.06 (t, $^1J_{C,H}$ = 140.8 Hz, CH_2O), 70.44 (CH_2O), 70.50 (4 CH_2O), 71.81 (t, $^1J_{C,H}$ = 144.1 Hz, CH_2CH_2I), 107.06 [d, $^1J_{C,H}$ = 159.6 Hz, C(5)], 108.36 [d, $^1J_{C,H}$ = 160.1 Hz, C(2)], 125.27 [dd, $^2J_{C,H}$ = 23.5, $^3J_{C,H}$ = 7.2 Hz, C(1)], 129.33 [d, $^1J_{C,H}$ = 153.1 Hz, C(6)], 145.41 and 145.56 [C(3), C(4)], 190.18 (d, $^1J_{C,H}$ = 169.8 Hz, CH=O) ppm. IR (film on KBr): $\tilde{\nu}$ = 3380 (br., N-H), 1670 (C=O) cm^{-1}. MS (EI, 70 eV): *m/z* = 481 (15) [M^+], 199 (8), 178 (8), 177 (6), 155 (100), 151 (35), 150 (31), 148 (7), 128 (10), 122 (6), 63 (6). HRMS calcd. for $C_{18}H_{28}INO_6$ [M^+] 481.0959, found 481.0947.

Synthesis of Benzoazacrown Ethers 5a−c and 6a−c (General Procedure): A mixture of iodide **4a−c** (0.15 mmol) and dry M_2CO_3 (M = Li, Na, K, Rb, Cs; 1.5 mmol) in dry MeCN (5 mL) was heated at 100 °C (a water bath) in a sealed tube for 150 h. After tube opening, the inorganic solid was filtered off, the solvent was evaporated, and the residue was purified by column chromatography on silica gel to separate unchanged **4** and a mixture of azacrown ethers **5** and **6** using a 1:1 benzene/EtOAc solvent system in the case of **5a** and **6a** and EtOAc in the case of **5b** and **6b**. For azacrown ethers **5c** and **6c**, column chromatography on silica gel (EtOAc, then EtOAc/EtOH, 5:1) was employed for the separation, and additional purification was achieved by passing the mixture of **5c** and **6c** through a small layer of Al_2O_3 (Merck, 0.063−0.200 mm, neutral, Typ E) by using EtOAc as an eluent. Percentages of the recovered iodides **4a−c** and the yields of azacrown ethers **5a−c** and **6a−c** calculated from ^1H NMR spectra of the purified mixtures are presented in Table 1.

Synthesis of Benzoazacrown Ethers 5b and 6b in the Presence of 1,8-Bis(dimethylamino)naphthalene: A mixture of iodide **4b** (66 mg, 0.15 mmol) and BDN (39 mg, 0.18 mmol) in dry MeCN (5 mL) was heated at 100 °C (a water bath) in a sealed tube for 150 h. After tube opening, the solvent was evaporated, 5% aqueous HCl (100 mL) was added to the residue, and the system was extracted with $CHCl_3$. The solvent was evaporated from the extract and the residue was purified according to the general procedure. The percentage of the recovered iodide **4b** and the yields of benzoazacrown ethers **5b** and **6b** calculated from the ^1H NMR spectrum of the purified mixture are presented in Table 1.

Separation of Benzoazacrown Ethers 5a−c and 6a−c (General Procedure): The purified mixture of **5** and **6** was separated by column chromatography on silica gel (first a benzene/EtOAc/AcOH, 1:1:2 or a EtOAc/AcOH, 1:1) to elute **6a** or **6b,c**, respectively, and then with EtOAc to give **5a−c**. After evaporation of the fraction containing benzoazacrown ether **6**, 5% aqueous Na_2CO_3 was added to the residue and the system was extracted with benzene. The extract was washed with water and concentrated to yield **6a−c**.

Compound 5a: 5a was isolated as a white solid. M.p. 71−72 °C (hexane). ^1H NMR ($CDCl_3$, 25 °C): δ = 2.90 (s, 3 H, MeN), 3.53 (t, $^3J_{H,H}$ = 6.5 Hz, 2 H, CH_2N), 3.74 (m, 2 H, CH_2O), 3.77 (m, 2 H, CH_2O), 3.90 (t, $^3J_{H,H}$ = 6.5 Hz, 2 H, CH_2CH_2N), 3.94 (m, 2 H, CH_2CH_2OAr), 4.19 (m, 2 H, CH_2OAr), 6.86 [d, $^3J_{H,H}$ = 8.2 Hz, 1 H, C(11)-H], 7.32 [d, $^4J_{H,H}$ = 1.5 Hz, 1 H, C(14)-H], 7.37 [dd, $^3J_{H,H}$ = 8.2, $^4J_{H,H}$ = 1.5 Hz, 1 H, C(12)-H], 9.76 (s, 1 H, CH=O) ppm. ^{13}C NMR ($CDCl_3$, 25 °C): δ = 39.58 (q, $^1J_{C,H}$ = 135.6 Hz, MeN), 54.77 (t, $^1J_{C,H}$ = 135.7 Hz, CH_2N), 68.48 (t, $^1J_{C,H}$ = 141.1 Hz, CH_2OAr), 68.54 (t, $^1J_{C,H}$ = 144.1 Hz, CH_2CH_2OAr), 69.27 (t, $^1J_{C,H}$ = 142.5 Hz, CH_2CH_2N), 69.84 (t, $^1J_{C,H}$ = 140.7 Hz, CH_2O), 71.76 (t, $^1J_{C,H}$ = 141.3 Hz, CH_2O), 110.70 [d, $^1J_{C,H}$ = 159.3 Hz, C(14)], 115.50 [d, $^1J_{C,H}$ = 158.6 Hz, C(11)], 127.07 [dd, $^1J_{C,H}$ = 159.9, $^3J_{C,H}$ = 6.5 Hz, C(12)], 128.71 [d, $^2J_{C,H}$ = 25.2 Hz, C(13)], 147.95 and 150.19 [C(14a), C(10a)], 190.54 (d, $^1J_{C,H}$ = 171.3 Hz, CH=O) ppm. IR (film on KBr): $\tilde{\nu}$ = 1675 (C=O) cm^{-1}. MS (EI, 70 eV): *m/z* = 265 (88) [M^+], 234 (78), 208 (60), 190 (47), 178 (58), 177 (88), 176 (95), 164 (100), 163 (52), 162 (91), 148 (50). HRMS calcd. for $C_{14}H_{19}NO_4$ [M^+] 265.1314, found 265.1380. $C_{14}H_{19}NO_4$ (265.31): calcd. C 63.38, H 7.22, N 5.28; found C 63.21, H 7.31, N 5.21.

Compound 6a: 6a was isolated as a light yellow oil. ^1H NMR ($CDCl_3$, 25 °C): δ = 3.38 (q, $^3J_{H,H}$ = 5.1 Hz, 2 H, CH_2N), 3.60 (m, 2 H, CH_2O), 3.64 (m, 2 H, CH_2CH_2OAr), 3.69 (m, 2 H, CH_2O), 3.77 (t, $^3J_{H,H}$ = 4.9 Hz, 2 H, CH_2CH_2N), 4.21 (m, 2 H, CH_2OAr), 6.47 (br. t, 1 H, NH), 6.63 (d, $^3J_{H,H}$ = 8.7 Hz, 1 H, C(11)-H], 7.48 [dd, $^3J_{H,H}$ = 8.7, $^4J_{H,H}$ = 1.5 Hz, 1 H, C(12)-H], 7.49 [d, $^4J_{H,H}$ = 1.5 Hz, 1 H, C(14)-H], 9.68 (s, 1 H, CH=O) ppm. ^{13}C NMR ($CDCl_3$, 25 °C): δ = 42.85 (t, $^1J_{C,H}$ = 137.0 Hz, CH_2N), 68.96 (t, $^1J_{C,H}$ = 141.2 Hz, CH_2CH_2OAr), 69.04 (t, $^1J_{C,H}$ = 140.4 Hz, CH_2CH_2N), 69.92 (t, $^1J_{C,H}$ = 141.0 Hz, CH_2O), 70.08 (t, $^1J_{C,H}$ = 142.5 Hz, CH_2O), 72.82 (t, $^1J_{C,H}$ = 145.1 Hz, CH_2OAr), 109.24 [dd, $^1J_{C,H}$ = 158.5, $^2J_{C,H}$ = 5.8 Hz, C(11)], 119.01 [d, $^1J_{C,H}$ = 153.7 Hz, C(12)], 125.68 [dd, $^2J_{C,H}$ = 23.0, $^3J_{C,H}$ = 8.1 Hz, C(13)], 130.16 [d, $^1J_{C,H}$ = 163.1 Hz, C(14)], 145.81 and 147.97 [C(14a), C(10a)], 189.97 (d, $^1J_{C,H}$ = 170.4 Hz, CH=O) ppm. IR (film on KBr): $\tilde{\nu}$ = 3350 (br., N-H), 1674 (C=O) cm^{-1}. MS (EI, 70 eV): *m/z* = 251 (100) [M^+], 194 (33), 176 (80), 163 (34), 162 (65), 150 (95), 149 (35), 148 (100), 65 (31), 58 (38), 51 (25). HRMS calcd. for $C_{13}H_{17}NO_4$ [M^+] 251.1157, found 251.1183.

Compound 5b: 5b was isolated as a white solid. M.p. 50−51 °C (hexane). ^1H NMR ($CDCl_3$, 25 °C): δ = 2.93 (s, 3 H, MeN), 3.43 (t, $^3J_{H,H}$ = 7.4 Hz, 2 H, CH_2N), 3.69 (s, 4 H, 2 CH_2O), 3.71 (s, 4 H, 2 CH_2O), 3.92 (m, 2 H, CH_2CH_2OAr), 3.95 (t, $^3J_{H,H}$ = 7.4 Hz, 2 H, CH_2CH_2N), 4.20 (m, 2 H, CH_2OAr), 6.85 [d, $^3J_{H,H}$ = 8.2 Hz, 1 H, C(14)-H], 7.30 [d, $^4J_{H,H}$ = 1.5 Hz, 1 H, C(17)-H], 7.35 [dd, $^3J_{H,H}$ = 8.2, $^4J_{H,H}$ = 1.5 Hz, 1 H, C(15)-H], 9.75 (s, 1 H, CH=O) ppm. ^{13}C NMR ($CDCl_3$, 25 °C): δ = 40.03 (q, $^1J_{C,H}$ = 135.8 Hz, MeN), 54.85 (t, $^1J_{C,H}$ = 138.6 Hz, CH_2N), 67.86 (t, $^1J_{C,H}$ = 143.7 Hz, CH_2OAr), 68.88 (t, $^1J_{C,H}$ = 142.4 Hz, CH_2CH_2N), 69.21 (t, $^1J_{C,H}$ = 142.2 Hz, CH_2CH_2OAr), 69.60 (t, $^1J_{C,H}$ = 140.5 Hz, CH_2O), 69.75 (t, $^1J_{C,H}$ = 141.3 Hz, CH_2O), 69.86 (t, $^1J_{C,H}$ = 140.5 Hz, CH_2O), 70.64 (t, $^1J_{C,H}$ = 141.7 Hz, CH_2O), 109.31 [d, $^1J_{C,H}$ = 156.4 Hz, C(17)], 115.44 [d, $^1J_{C,H}$ = 159.1 Hz, C(14)], 127.01 [dd, $^1J_{C,H}$ = 160.7, $^3J_{C,H}$ = 6.2 Hz, C(15)], 128.71 [dd, $^2J_{C,H}$ = 23.9, $^3J_{C,H}$ = 8.9 Hz, C(16)], 147.87 and 150.11 [C(17a), C(13a)], 190.61 (d, $^1J_{C,H}$ = 171.5 Hz, CH=O) ppm. IR (film on KBr): $\tilde{\nu}$ = 1675 (C=O) cm^{-1}. MS (EI, 70 eV): *m/z* = 309 (34) [M^+], 178 (43), 177 (39), 176 (36), 165 (40), 164 (96), 163 (78), 162 (100), 148 (37), 77 (32), 65 (49). HRMS calcd. for $C_{16}H_{23}NO_5$ [M^+] 309.1576, found 309.1653. $C_{16}H_{23}NO_5$ (309.36): calcd. C 62.12, H 7.49, N 4.53; found C 62.15, H 7.54, N 4.52.

Compound 6b: 6b was isolated as a light yellow oil. ^1H NMR ($CDCl_3$, 25 °C): δ = 3.35 (q, $^3J_{H,H}$ = 4.7 Hz, 2 H, CH_2N),

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3.65−3.71 (m, 6 H, 3 CH_2O), 3.73 (m, 2 H, CH_2O), 3.80 (t, $^3J_{H,H}$ = 4.9 Hz, 2 H, C$H_2$$CH_2N$), 3.87 (m, 2 H, C$H_2$$CH_2OAr$), 4.18 (m, 2 H, C$H_2$OAr), 5.86 (br. t, 1 H, NH), 6.55 [d, $^3J_{H,H}$ = 8.1 Hz, 1 H, C(14)-H], 7.26 [s, 1 H, C(17)-H], 7.37 [d, $^3J_{H,H}$ = 8.1 Hz, 1 H, C(15)-H], 9.68 (s, 1 H, CH=O) ppm. ^{13}C NMR ($CDCl_3$, 25 °C): δ = 42.31 (t, $^1J_{C,H}$ = 136.7 Hz, CH_2N), 67.88 (t, $^1J_{C,H}$ = 144.5 Hz, CH_2OAr), 68.30 (t, $^1J_{C,H}$ = 141.2 Hz, CH_2CH_2N), 69.01 (t, $^1J_{C,H}$ = 141.7 Hz, CH_2CH_2OAr), 69.84 (t, $^1J_{C,H}$ = 140.1 Hz, CH_2O), 69.92 (t, $^1J_{C,H}$ = 140.5 Hz, CH_2O), 70.00 (t, $^1J_{C,H}$ = 141.1 Hz, CH_2O), 70.18 (t, $^1J_{C,H}$ = 141.9 Hz, CH_2O), 107.60 [dd, $^1J_{C,H}$ = 159.4, $^2J_{C,H}$ = 5.3 Hz, C(14)], 108.58 [d, $^1J_{C,H}$ = 158.9 Hz, C(17)], 125.58 [dd, $^2J_{C,H}$ = 23.5, $^3J_{C,H}$ = 7.4 Hz, C(16)], 129.37 [d, $^1J_{C,H}$ = 164.4 Hz, C(15)], 145.17 and 145.86 [C(17a), C(13a)], 190.34 (d, $^1J_{C,H}$ = 169.9 Hz, CH=O) ppm. IR (film on KBr): $\tilde{\nu}$ = 3400 (br., N-H), 1670 (C=O) cm^{-1}. MS (EI, 70 eV): *m/z* = 295 (96) [M^+], 238 (15), 194 (16), 176 (56), 164 (17), 163 (13), 162 (27), 151 (14), 150 (100), 149 (32), 148 (81). HRMS calcd. for $C_{15}H_{21}NO_5$ [M^+] 295.1420, found 295.1417.

Compound 5c: 5c was isolated as a light yellow oil after extraction with boiling hexane. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 3.02 (s, 3 H, MeN), 3.59 (t, $^3J_{H,H}$ = 6.0 Hz, 2 H, CH_2N), 3.62−3.68 (m, 8 H, 4 CH_2O), 3.71 (m, 4 H, 2 CH_2O), 3.83 (t, $^3J_{H,H}$ = 6.0 Hz, 2 H, C$H_2$$CH_2N$), 3.93 (m, 2 H, C$H_2$$CH_2OAr$), 4.21 (m, 2 H, C$H_2$OAr), 6.85 [d, $^3J_{H,H}$ = 8.2 Hz, 1 H, C(17)-H], 7.32 [d, $^4J_{H,H}$ = 1.7 Hz, 1 H, C(20)-H], 7.37 [dd, $^3J_{H,H}$ = 8.2, $^4J_{H,H}$ = 1.7 Hz, 1 H, C(18)-H], 9.76 (s, 1 H, CH=O) ppm. ^{13}C NMR ($CDCl_3$, 25 °C): δ = 40.76 (q, $^1J_{C,H}$ = 136.2 Hz, MeN), 54.42 (t, $^1J_{C,H}$ = 137.0 Hz, CH_2N), 67.44 (t, $^1J_{C,H}$ = 143.9 Hz, CH_2OAr), 69.45 (t, $^1J_{C,H}$ = 140.3 Hz, CH_2CH_2OAr), 70.09 (t, $^1J_{C,H}$ = 141.3 Hz, CH_2O), 70.42 (t, $^1J_{C,H}$ = 142.3 Hz, CH_2CH_2N), 70.54 (t, $^1J_{C,H}$ = 139.0 Hz, CH_2O), 70.66 (t, $^1J_{C,H}$ = 140.4 Hz, CH_2O), 70.71 (t, $^1J_{C,H}$ = 140.4 Hz, CH_2O), 71.02 (t, $^1J_{C,H}$ = 141.6 Hz, CH_2O), 71.25 (t, $^1J_{C,H}$ = 140.6 Hz, CH_2O), 109.83 [dd, $^1J_{C,H}$ = 157.7, $^3J_{C,H}$ = 5.0 Hz, C(20)], 115.65 [d, $^1J_{C,H}$ = 159.0 Hz, C(17)], 127.03 [dd, $^1J_{C,H}$ = 160.5, $^3J_{C,H}$ = 5.6 Hz, C(18)], 128.59 [dd, $^2J_{C,H}$ = 23.7, $^3J_{C,H}$ = 7.9 Hz, C(19)], 147.52 and 149.80 [C(20a), C(16a)], 190.56 (d, $^1J_{C,H}$ = 171.2 Hz, CH=O) ppm. IR (film on KBr): $\tilde{\nu}$ = 1672 (C=O) cm^{-1}. MS (EI, 70 eV): *m/z* = 353 (17) [M^+], 190 (19), 177 (39), 176 (32), 164 (100), 163 (25), 162 (71), 151 (26), 148 (22), 65 (21), 58 (43). HRMS calcd. for $C_{18}H_{27}NO_6$ [M^+] 353.1838, found 353.1863. $C_{18}H_{27}NO_6$ (353.41): calcd. C 61.17, H 7.70, N 3.96; found C 61.22, H 7.26, N 4.16.

Compound 6c: 6c was isolated as a yellowish solid. M.p. 65−67 °C (hexane). ^{1}H NMR ($CDCl_3$, 25 °C): δ = 3.42 (br. q, $^3J_{H,H}$ = 4.5 Hz, 2 H, CH_2N), 3.63−3.71 (m, 12 H, 6 CH_2O), 3.75 (t, $^3J_{H,H}$ = 4.7 Hz, 2 H, C$H_2$$CH_2N$), 3.88 (m, 2 H, C$H_2$$CH_2OAr$), 4.21 (m, 2 H, C$H_2$OAr), 6.52 [d, $^3J_{H,H}$ = 8.2 Hz, 1 H, C(17)-H], 6.73 (br. t, 1 H, NH), 7.22 [d, $^4J_{H,H}$ = 1.4 Hz, 1 H, C(20)-H], 7.34 [dd, $^3J_{H,H}$ = 8.2, $^4J_{H,H}$ = 1.4 Hz, 1 H, C(18)-H], 9.65 (s, 1 H, CH=O) ppm. ^{13}C NMR ($CDCl_3$, 25 °C): δ = 42.91 (t, $^1J_{C,H}$ = 136.5 Hz, CH_2N), 66.96 (t, $^1J_{C,H}$ = 143.7 Hz, CH_2OAr), 69.04 (t, $^1J_{C,H}$ = 143.9 Hz, CH_2CH_2N), 69.29 (t, $^1J_{C,H}$ = 141.5 Hz, CH_2CH_2OAr), 70.20 (CH_2O), 70.23 (CH_2O), 70.34 (t, $^1J_{C,H}$ = 140.7 Hz, 3 CH_2O), 70.44 (t, $^1J_{C,H}$ = 140.0 Hz, CH_2O), 107.00 [dd, $^1J_{C,H}$ = 158.4, $^3J_{C,H}$ = 4.8 Hz, C(17), C(20)], 125.04 [dd, $^2J_{C,H}$ = 23.6, $^3J_{C,H}$ = 7.4 Hz, C(19)], 129.41 [d, $^1J_{C,H}$ = 160.6 Hz, C(18)], 144.85 and 145.83 [C(20a), C(16a)], 190.23 (d, $^1J_{C,H}$ = 169.3 Hz, CH=O) ppm. IR (film on KBr): $\tilde{\nu}$ = 3421 (br., N-H), 1672 (C=O) cm^{-1}. MS (EI, 70 eV): *m/z* = 340 (18), 339 (83) [M^+], 176 (68), 164 (17), 163 (21), 162 (26), 150 (100), 149 (22), 148 (75), 65 (17), 58 (32). HRMS calcd. for $C_{17}H_{25}NO_6$ [M^+] 339.1682, found 339.1689. $C_{17}H_{25}NO_6 \cdot H_2O$ (357.40): calcd. C 57.13; H 7.61; N 3.92; found C 57.78, H 7.31, N 3.87.

Demethylation of Benzoazacrown Ether 5c: A solution of **5c** (9 mg, 0.025 mmol) in a 1:1 (v/v) mixture of EtOAc/AcOH (6 mL) was refluxed for 80 h. The solvent was evaporated and the residue was purified by column chromatography on silica gel using first a 1:1 benzene/EtOAc solvent system and then EtOAc as the eluent to give benzoazacrown ether **6c** (3 mg, 35%) as a light yellow oil.

X-ray Crystallographic Study: Crystals of **5a** and **6c** suitable for X-ray crystallography were grown by slow evaporation from hexane and heptane/CH_2Cl_2 solutions, respectively. The structures were solved by direct methods and refined by full-matrix least-squares on F^2 in the anisotropic approximation for all non-hydrogen atoms. The hydrogen atoms were located from difference Fourier synthesis and refined isotropically. The SHELXS-86[20] and SHELXL-97[21] software were used for structure solution and refinement, respectively. Crystallographic data and structure solution and refinement parameters are given in Table 2. CCDC-195278 (**5a**) and CCDC-195280 (**6c**) contain the supplementary crystallographic data (excluding structure factors) for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) +44−1223/336−033; E-mail: deposit@ccdc.cam.ac.uk].

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